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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,333	12/03/2001	Kathleen D. Danenberg	11220/146	5598

23838 7590 09/01/2005

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER
	08302005

DATE MAILED:

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Commissioner for Patents

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/998,333	**Applicant(s)** DANENBERG, KATHLEEN D.	
	Examiner Young J. Kim	**Art Unit** 1637	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 August 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *18 August 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,5,17,20,24,25 and 27*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 5. Applicant's reply has overcome the following rejection(s): by entry of the amendment, Applicants have overcome the rejection of claims 1 and 5 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Final Action mailed on February 18, 2005. It should be noted that the rejection under 35 U.S.C. 112, second paragraph is not a written description rejection as applicants appeared to have conveyed.

Continuation of 11. does NOT place the application in condition for allowance because: Applicants' request for the amendment for entry of the application serial number 09/988,784 and its incorporation by reference is found persuasive. Applicants' arguments drawn to the rejection of claims 1, 5, 17, 20, 24, 25, and 27 under 35 U.S.C. 112, first paragraph, for lack of enablement have been fully considered but they are not persuasive for the following reasons. With regard to the rejection of claim 26, which was also included in the Final Office Action mailed on February 18, 2005, has been canceled by Applicants' Amendment received on August 18, 2005.
Applicants contend that the present invention provides a method to determine an appropriate chemotherapeutic regimen for treating metastatic tumors based upon the level of tumor gene expression from a patient derived primary tumor sample (page 6, 2nd paragraph, Response). Applicants contend that the present invention provides a method to determine the level of EGFR expression from a patient derived primary tumor sample and that the uncorrected gene expression for EGFR and normalizing UGE with known relative EGFR expression levels can be calculated using the equations as provided in Example 3 of the specification. Applicants further contend that the determination of the corrected, "relative ECFR [sic]" (assuming EGFR) is also provided on page 29 of the instant specification (page 6, 3rd paragraph, Response).

The arguments are not found persuasive.
Claims are drawn to a method of determining a chemotherapeutic regimen for treating a *metastatic tumor* in an individual having a primary and metastatic tumor, wherein the expression of EGFR levels in the primary tumor is assessed for determining whether the regimen will be successful or not. Hence, the skilled artisan, in order to practice the invention as claimed (the use criteria within Enablement), must have some sort of correlation between the expression of EGFR level in primary tumor as compared to that from metastatic tumor.
The instant specification stresses the importance as well:
"Differential gene expression between a tumor and its metastases not only underlies the mechanism of tumor metastasis, but more importantly to the clinician, it determines the efficacy of chemotherapeutic agents on primary tumor and matched metastases. Whereas primary tumor specimens are generally available either as pre-treatment paraffin-embedded biopsies or as resection specimens, in many cases, and especially in earlier stages of cancer, metastases are not readily detectable and biopsy specimens of matched tumor metastases on which phenotypic analyses could be performed would thus not be available. **Therefore, it is important to determine the degree of variation of gene expression between primary tumors and metastases. This information is vital in order to determine whether or not a particular chemotherapeutic would be an effective therapeutic against the both the primary tumor as well as the metastases.**" (page 8, lines 4-15).
The specification even goes on to say that, "[c]urrently, the only way to reach such a conclusion was to have a fresh or frozen tissue biopsy of primary tumor and matching tumor metastases" evidencing that in order to **determine the degree of variation of gene expression between primary tumors and metastases.**
The specification, however, absolutely lacks this critically important data. The only description which Applicants rely on is found on page 22 of the specification where it is stated that, "a primary tumor having high level of EGFR mRNA expression is **considered likely** to be sensitive to receptor tyrosine kinase targeted chemotherapy. The specification states that, "[t]hus, with the present invention, the tumor metastases of patients whose primary tumors express high levels, i.e., above a predetermined threshold value, of EGFR mRNA are considered also likely to be sensitive to receptor tyrosine kinase target chemotherapy." (page 22, lines 15-19). The specification merely speculates that the expression of EGFR in primary tumor is correlated with its level of expression in the matching tumor metastases. But other than this statement, the specification absolutely fails to described to a skilled artisan how the levels are correlated **nor** what the "threshold value" is.
With regard to Example 3 that Applicants are referring to, the arguments are not found persuasive for the following reasons.
Example 3, merely gives example of determining the uncorrected gene expression (UGE) for EGFR in a test sample and calibration sample by using an internal control beta-actin (page 38, bottom paragraph). The example only gives guidance in calculating the corrected relative EGFR expression in an unknown sample by multiplying UGE with the correction factor derived from internal control (page 39, lines 14-18). The example does not give any correlation between the level of expression of EGFR in primary tumor and its level of expression in metastasis, so as to allow a skilled artisan to determine a chemotherapeutic regimen for treating a **metastatic tumor** based on the expression of EGFR in primary tumor sample.
With regard to Applicants' contention that Applicants have adequately provided in the specification that expression levels between primary tumors and metastatic tumors are similar (page 6, 3rd paragraph, Response), Applicants' assertions are based on a couple of species of genes which is embraced by genus embracing thousands of candidate genes. It is premature to assume that based on the small number of genes disclosed in the specification, one of skill in the art can assume that **any** gene which is differentially expressed in primary tumor is also similarly differentially expressed in metastatic tumor. With regard to Applicants' contention that that there is no need to provide examples for every species, it is determined that absent this "important" piece of information, one skilled in the art cannot practice the invention as claimed without undue experimentation. If Applicants' assertions were true, then a **specification** teaching a method of diagnosing cancer by determining the expression level of gene B would enable a **claim** drawn to a method of diagnosing cancer by determining the expression level of gene A, wherein there is no teaching in the specification regarding whether gene A is differentially expressed in the tumor sample when compared against the normal sample. In order words, if "no-need-to-provide-examples-for-every species standard of Applicants is applied, such method would also be enabling. However, such would not be the case.
It is determined that some correlation between the level of EGFR in primary tumor and metastatic tumor is required to enable a skilled artisan.

8-30-05
YOUNG J. KIM
PATENT EXAMINER

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
6/30/05